ATORVASTATIN CALCIUM TABLETS

Amlodipine besylate/Atorvastatin calcium

5 mg/ 10 mg, 5 mg/ 20 mg, 5 mg/ 40 mg, 10 mg/ 10 mg, 10 mg/ 20 mg, 10 mg/ 40 mg Film coated tablets

Rx Only

Reference Product: US

AIME Markets using same as LPD:

Bahrain, Jordan, Kuwait, Lebanon, Oman, Qatar,UAE

US Prescribing Information and Medication Guide

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CADUET safely and effectively. See full prescribing information for CADUET.

CADUET® (amlodipine besylate and atorvastatin calcium) tablets, for oral use

----------INDICATIONS AND USAGE----------

CADUET is a combination of amlodipine, a dihydropyridine calcium channel blocker, and atorvastatin calcium, a HMG CoA-reductase inhibitor, indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine is indicated for the treatment of hypertension, to lower blood pressure. [1] Hypertension increases the risk for fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Amlodipine is indicated for the treatment of Coronary Artery Disease (CAD). [2]

Atorvastatin is indicated as an adjunct therapy to diet for prevention of cardiovascular events in patients with CAD, risk factors for CAD, and

----------DOSAGE AND ADMINISTRATION----------

	Usual starting dose (mg daily)	Maximum dose (mg daily)
Amlodipine	5*	10
Atorvastatin	10-20*	80

* Start small adults or children, fragile, or elderly patients, or patients with hepatic insufficiency. See text for dosing details.

† Start patients requiring large LDL-C reduction (> 45%) at 40 mg once daily.

----------DOSAGE FORMS AND STRENGTHS----------

Tablets contain amlodipine besylate equivalent to amlodipine 2.5, 5, or 10 mg, and atorvastatin calcium equivalent to atorvastatin 10, 20, 40, or 80 mg.[3].

----------CONTRAINDICATIONS----------

- Active liver disease (4)
- Pregnancy (4)
- Lactation (4)

----------WARNINGS AND PRECAUTIONS----------

- Myopathy and Rhabdomyolysis: Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. CADUET therapy should be discontinued if myopathy is diagnosed or suspected (5.1, 8.5).
- Hepatic Toxicity: Monitor liver enzymes before and during treatment (5.2)
- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Use with caution in patients with coronary artery or ischemic heart disease (5.3).
- Angina or myocardial infarction may occur after initiation or dose increase (5.3).

----------ADVERSE REACTIONS----------

Most common adverse reaction (3% greater than placebo) to amlodipine is edema (6.1).

Most common adverse reactions leading to atorvastatin discontinuation were myalgia and rhabdomyolysis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer or report any suspected adverse reactions according to your local country requirements.

----------DRUG INTERACTIONS----------

Increased Risk of Myopathy/Rhabdomyolysis (2.5, 5.1, 7, 12.3)	
Cyclosporine, HIV protease inhibitors (lopinavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
Lopinavir plus ritonavir	Use lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily
Other Lipid-Lowering Medications: Increased risk of myopathy (7)	
• Rifampin: Take at same time as CADUET (7.9).	
• Digoxin: Monitor digoxin levels (7.10).	
• Oral Contraceptives: Norethindrone and ethinyl estradiol may be increased (7.11).	

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic Impairment: Plasma concentrations of atorvastatin markedly increased in patients with active liver disease (8.6, 12.3).
- Females of reproductive potential: Advise females of reproductive potential to use effective contraception in combination with CADUET (8.1).

See 17 for Patient Counseling INFORMATION and patient labeling.

Revised: 9/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CADUET (amlodipine and atorvastatin) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine

1.1 Hypertension

Amlodipine is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including amlodipine.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For the majority of patients with hypertension, it has been published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC), available.

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per unit of pressure is greater at higher pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and relatively less in patients at lower risk but still at high absolute risk from treatment to a lower blood pressure goal.

Some antihypertensive drugs have additional blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved labeled indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Amlodipine may be used alone or in combination with other antihypertensive agents.

1.2 Coronary Artery Disease (CAD)

Chronic Stable Angina

Amlodipine is indicated for the symptomatic treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina)

Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal agents.

Angiographically Documented CAD

In patients with recently documented CAD by angiography and without heart failure or an ejection fraction < 40%, amlodipine administration does not raise the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure.

Atorvastatin

Therapy with HMG CoA-reductase inhibitors (lipid-altering agents) should be only one component of multiple risk factor intervention in individuals at risk for atherosclerotic vascular disease (CVD) and myocardial infarction (MI). Pharmacological therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic interventions has been inadequate. In patients with coronary heart disease (CHD) or multiple risk factors for CHD, atorvastatin calcium is indicated concomitantly with diet therapy.

1.3 Prevention of Cardiovascular Disease (CVD) in Adults

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C), or a family history of early coronary heart disease, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk of revascularization procedures and angina

In adult patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease, but with no clinically evident coronary heart disease such as age, smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C), or a family history of early coronary heart disease, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

1.4 Hyperlipidemia

Atorvastatin is indicated:

- As an adjunct to diet to reduce elevated total cholesterol (total-C), cholesterol bound to low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) and to increase HDL-C in adult patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb).
- As an adjunct to diet for the treatment of adult patients with elevated serum TG levels (Fredrickson Type IV).
- As an adjunct to diet for the treatment of adult patients with dysbetalipoproteinemia (Fredrickson Type III) who have inadequate response to diet.
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in pediatric patients, 10 years of age or older, with heterozygous familial hypercholesterolemia (HeFH) if after an adequate trial of diet therapy the following findings are present:
  - a. LDL-C remains ≥ 190 mg/dL or
  - b. LDL-C remains ≥ 160 mg/dL and:
  - i. there is a positive family history of premature CVD or
  - ii. two or more other CVD risk factors are present in the pediatric patient

1.5 Limitations of Use

Atorvastatin has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).

2 DOSAGE AND ADMINISTRATION

CADUET

Dosage of CADUET must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertensive/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently.

CADUET may be substituted for its individually titrated components. Patients may be given the equivalent dose of CADUET or a dose of CADUET with increase amount of amlodipine, atorvastatin, or both for additional antianginal effects, blood pressure lowering, or lipid-lowering effect.

CADUET may be used as initial combination therapy in patients already on one of its components. CADUET may be used to initiate treatment in patients with hypertension and hypercholesterolemia or angina.

Amlodipine

The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily, and the maximum dose is 10 mg once daily.

Pediatric (age > 6 years), small adult, fragile, or elderly patients, or patients with hepatic insufficiency: Dosing may be started on 2.5 mg once daily and may be used when adding amlodipine to other antihypertensive therapy.

Adjust dosage according to blood pressure response. In general, wait 7 to 14 days between titration steps. Titration may proceed more rapidly, however, if clinically warranted, if blood pressure is assessed frequently.

Angina: The recommended dose of amlodipine for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested for the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Coronary Artery Disease: The recommended dose range of amlodipine for patients with CAD is 5-10 mg once daily. In clinical trials, the majority of patients required 10 mg *[see Clinical Studies (14.4)]*.

Pediatrics: The effective antihypertensive oral dose of amlodipine in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients *[see Clinical Pharmacology (12.3), Clinical Studies (14.7)]*.

Atorvastatin (Hyperlipidemia)

Hyperlipidemia and Mixed Dyslipidemia: The recommended starting dose of atorvastatin is 10 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10 to 80 mg daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. Dose adjustments should be made according to blood lipids and lipoprotein levels, taking into account the patient characteristics such as goal of therapy and response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 3 to 4 weeks and dosage adjusted accordingly.

Homozygous Familial Hypercholesterolemia: The dosage range of atorvastatin in patients with HoFH is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering therapies (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Concomitant Lipid-Lowering Therapy: Atorvastatin may be used with bile acid resins. Modify dose of atorvastatin promptly in patients receiving the combination of HMG-CoA reductase inhibitors (statins) and fibrates *[see Warnings and Precautions (5.1), Drug Interactions (7.6)]*.

*Patients with Renal Impairment: Renal disease does not affect the plasma concentrations and LDL-C effect of atorvastatin. Therefore, dose adjustment in patients with renal dysfunction is not necessary *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.*

Use with Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors: Avoid atorvastatin, cyclosporine or the HIV protease inhibitors (lopinavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), avoid therapy with atorvastatin and clarithromycin in patients with HoFH, lopinavir plus ritonavir, use the lowest necessary dose of atorvastatin. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, limit therapy with atorvastatin to 20 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary for patient response is employed. Consider taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, limit therapy with atorvastatin to 40 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary for atorvastatin is employed *[see Warnings and Precautions (5.1), Drug Interactions (7)]*.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 Years to 17 Years of Age): The recommended starting dose of atorvastatin is 10 mg/day; the usual dose range is 10 to 20 mg daily once daily *[see Clinical Studies (14.11)]*. Doses should be individualized according to the recommended goal of therapy *[see Indications and Usage (1.4) and Clinical Pharmacology (12)]*. Adjustments should be made at intervals of 4 weeks or more.

3 DOSAGE FORMS AND STRENGTHS

CADUET tablets are formulated for oral administration in the following strength combinations:

Table 1

	Atorvastatin (mg)			
	10	20	40	80
Amlodipine (mg) 2.5	X	X	X	X
5	X	X	X	X
10	X	X	X	X

Combinations of atorvastatin with 2.5 mg and 5 mg amlodipine are film-coated white, and combinations of atorvastatin with 10 mg amlodipine are film-coated blue.

4 CONTRAINDICATIONS

- **Active Liver Disease, Which May Include Unexplained Persistent Elevations in Hepatic Transaminase Levels**
- **Pregnancy** *[see Use in Specific Populations (8.1)]*
- **Lactation** *[see Use in Specific Populations (8.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. These patients deserve closer monitoring for skeletal muscle effects.

Rare reports exist of statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values; these myopathies should be considered when the concomitant use of higher doses of atorvastatin with certain drugs such as gemfibrozil and other fibrates, cyclosporine, lipid-lowering drugs, nicotinic acid, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, or marked elevation of CPK. Patients should be advised to report to their physicians if unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing CADUET. CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with statins is increased with concomitant administration of CYP3A4 inhibitors (or their transporter inhibitors), with advanced age (≥ 65 years), with uncontrolled hypothyroidism, with HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, fosamprenavir plus ritonavir, darunavir plus ritonavir, tipranavir plus ritonavir, fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combination therapy with CADUET and other lipid-lowering erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness in the days or weeks after the start of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with other myopathic drugs *[see Drug Interactions (7)]*. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

CADUET must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin therapy should be discontinued throughout the duration of fusidic acid treatment. There have reports of rhabdomyolysis (including some fatal cases) in patients receiving fusidic acid and statins in combination *[see section 4.5]*. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be temporarily withheld for the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of CADUET and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Prescribing recommendations for interacting agents are summarized in *Table 2 [see Dosage and Administration (2), Contraindications (4) and Clinical Pharmacology (12.3)]*.

Table 2. Atorvastatin Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Cyclosporine, HIV protease inhibitors (lopinavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

* Use with caution and with the lowest dose necessary (12.3)

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine *[see Drug Interactions (7.13)]*.

Withhold or discontinue in any patient with an acute, serious condition suggestive of a myopathy or predisposing for development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection; hypotension; major surgery; trauma; severe metabolic, endocrine, and electrolyte disorders; and uncontrolled seizures).

5.2 Liver Dysfunction

Statins, like atorvastatin, and some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (> 3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2, 0.2, 0.6, 0.8, 0.9, and 2.3% for 10, 20, 40, 80 mg atorvastatin. One patient in clinical trials with atorvastatin developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin and periodically thereafter. Patients who have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking other statins. Patients on statin therapy who develop any clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with CADUET, promptly interrupt therapy. If an alternate etiology is not found, do not restart CADUET.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of CADUET *[see Contraindications (4)]*.

5.3 Increased Angina and Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

5.4 Hypotension

Symptomatic hypotension is possible with use of amlodipine, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

5.5 Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Extensive evidence shows that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenocortical reserve. Its effect on testicular function has been studied in adequate numbers of patients, and it appears that atorvastatin's effect on spermatogenesis and fertility in adult male patients is not clinically significant. Adverse effects on sexual function in premenopausal women are unknown. Avoid a statin with drugs that may decrease the production of gonadal or adrenocorticosteroid hormones such ketoconazole, spironolactone, and cimetidine.

5.6 CNS Toxicity

Brain hemorrhage was seen in a female dog treated with atorvastatin for 3 months at 120 mg/kg/day (approximately 60 times the human exposure) were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating dosage to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC) for 80 mg/day and 11 times the human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated for 2 weeks at 120 mg/kg and the other given a 3-year study. No CNS lesions have been observed in mice after chronic administration of up to 500 mg/kg/day (at least 25 times the human AUC for up to 100 mg/day). There is no evidence of CNS lesions in rats given doses of 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose (MRHD) of 80 mg.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other statins. A chemically similar drug in this class produced optic nerve degeneration (optic neuropathy, presumed ischemic in etiology) in clinically normal dogs in a dose-dependent fashion at a dose thirty-times higher than the MRHD, based on a mg/m² basis (the mean drug level in humans taking the highest recommended dose).

5.7 Hemorrhagic Stroke

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, patients without CHD who had a stroke was administered in 4,731 subjects without CHD who had a stroke within the preceding 6 months. Patients in this study received atorvastatin 80 mg or placebo. In this post-hoc analysis, patients who were given atorvastatin 80 mg had a higher incidence of hemorrhagic stroke (59, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics of patients who had hemorrhagic stroke in the study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis and myopathy *[see Warnings and Precautions (5.1)]*
- Liver enzyme abnormalities *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

CADUET

CADUET (amlodipine besylate/atorvastatin calcium) has been evaluated for safety in 1,092 patients in double-blind placebo-controlled studies treated for co-morbid hypertension and hyperlipidemia. Treatment with CADUET was well tolerated. For the most part, adverse reactions have been mild or moderate in severity. Most adverse reactions in CADUET-treated patients were not related to the combination. Adverse reactions are similar to those of each component. The most common adverse reactions were those previously associated with amlodipine and atorvastatin.

The following information is based on the clinical experience with amlodipine and atorvastatin.

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy were of a nature that did not preclude continuing drug administration. Clinical trials designed specifically to examine the effect of amlodipine on mortality in patients (N=1,250), discontinuation of amlodipine because of adverse reactions was required in only about 1% of patients, and this was not different from placebo (about 1%). The most commonly reported side effects were frequent (more than 1 in 100 patients) edema. The incidence (%) of side effects that occurred in a dose-related manner are as follows:

The following information is based on the clinical experience with amlodipine.

	2.5 mg (N=275)	5 mg (N=276)	10 mg (N=268)	Placebo (N=520)
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.6

Other adverse reactions that were not clearly dose related but were reported at an incidence greater than 1.0% in placebo-controlled clinical trials are the following:

	Amlodipine (%) (N=1730)	Placebo (%) (N=1250)
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.1	0.4

Edema, flushing, palpitations, and somnolence appear to be more common in women than in men.

The following events occurred in < 1% but > 0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain. They are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including cardiac tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dysphagia, diarrhea, flatulence, gastritis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia,[1] back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps,[1] myalgia.

Psychiatric: sexual dysfunction (male[1] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea,[1] epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus,[1] rash,[1] skin erythematous, rash maculopapular.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

[1]These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total TG, TC, HDL-C, uric acid, blood urea nitrogen, or creatinine.

Atorvastatin

In the atorvastatin placebo-controlled clinical trial database of 16,066 patients (8,750 atorvastatin and 7,316 placebo), age ranging 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 2.7 years, 5.7% of patients were discontinued and 6.5% of the patients on placebo discontinued because of adverse reactions regardless of causality. The most common adverse reactions in patients treated with atorvastatin that led to treatment discontinuation and occurred at a frequency greater than placebo were: myalgia (0.8%), rash (0.6%), abdominal pain, asthenia, and nausea (0.4% each), and elevated liver enzymes (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) in controlled clinical trials in patients treated with atorvastatin were: dyspepsia (n=250) and arthralgia (8.3%), diarrhea (8.2%), pharyngitis (8.1%), pain in extremity (8.0%), and urinary tract infection (7.9%).

Table 3 summarizes the frequency of adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin for 1 year in placebo-controlled clinical trials.

Table 3. Clinical Adverse Reactions Occurring in ≥ 2% in Patients Treated with Atorvastatin and Occurring at an Incidence Greater than Placebo Regardless of Causality (% of Patients)

Adverse Reaction*	Atorvastatin 10 mg (N=2365)	Atorvastatin 20 mg (N=2306)	Atorvastatin 40 mg (N=1005)	Atorvastatin 80 mg (N=985)	Placebo (N=2737)
Nasopharyngitis	8.3	12.9	5.3	7.0	8.2
Arthralgia	6.9	10.8	5.7	10.5	7.6
Diarrhea	6.8	7.3	6.4	14.1	5.2
Pain in extremity	6.0	8.0	5.1	7.6	5.5
Urinary tract infection	5.7	6.9	6.4	8.0	4.1
Dyspepsia	4.7	5.9	3.2	6.0	3.3
Nausea	4.0	3.7	3.1	5.2	2.9
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3
Muscle spasms	3.6	4.6	4.8	5.1	2.4
Myalgia	3.5	5.0	3.2	6.4	2.3
Insomnia	3.0	2.8	1.1	5.3	2.8
Pharyngolaryngeal pain	2.9	3.1	2.1	2.8	2.7

* Adverse Reaction ≥ 2% in any dose greater than placebo.

Other adverse reactions reported in placebo-controlled studies include: dizziness, chest pain, peripheral edema, gastroenteritis, upper respiratory tract infection, sinusitis, flatulence, hepatitis, cholelithiasis. *Musculoskeletal system:* arthrosis, arthritis, leg cramps, neck pain, joint pain, joint swelling. *Metabolic and nutritional system:* transaminases increase, liver function test abnormal, blood creatine phosphokinase increase, hyperglycemia, glycosuria, hyperglycemia. *Nervous system:* nightmare, *Respiratory system:* epistaxis; *Skin and appendages:* urticaria; *Special senses:* vision blurred, tinnitus. *Urogenital system:* white blood cells urine positive.

Treating to New Targets Study (TNT)

In TNT [*See Clinical Studies (14.6)*] involving 10,001 subjects (age range: 21–93 years, 31% women, 94% Caucasians, 2% Asians, 1% Blacks, 3% other) with clinically evident CHD treated with atorvastatin 10 mg (n=4,995) or atorvastatin 80 mg (n=4,997) and followed for a median duration of 4.9 years, the incidence of adverse reactions was similar between the groups (13, 0.3%) compared to the low-dose atorvastatin group (8, 0.1%).

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4,731 subjects (age range 21–92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin 80 mg (n=2,365) or placebo (n=2,366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (3 or more times upper limit [>3 ULN] on 2 consecutive visits) in the atorvastatin group (9.5%) compared to placebo (0.1%). The incidence of LFTs > 3 ULN in the SPARCL study was similar between the groups (0.1%) compared atorvastatin and placebo, and the incidence of adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group *[see Warnings and Precautions (5.5)]*.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 30/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC[1]	Ratio of Cmax[2]
†Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	4.54	5.38
†Darunavir/r 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	3.45	2.25
†Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	40 mg SD	3.32	1.20
†Darunavir/r 300 mg BID/ritonavir 100 mg BID, 14 days	20 mg QD for 4 days	2.53	2.84
†Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	2.30	4.04
†Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	1.74	2.22
†Grapefruit Juice, 240 mL QD[4]	40 mg, SD	1.37	1.16
Diltiazem 240 mg QD, 28 days	40 mg, SD	1.51	1.00
Erythromycin 500 mg QID, 7 days	10 mg, SD	1.33	1.38
Amlodipine 10 mg, single dose	80 mg, SD	1.18	0.91
Cimetidine 300 mg QID, 7 weeks	10 mg QD for 2 weeks	1.00	0.89
Colestipol 10 g BID, 24 weeks	40 mg QD for 8 weeks	NA	0.74[5]
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	0.66	0.67
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	0.59	0.11
*Rifampin 600 mg QD, 7 days (co-administered)[6]	40 mg SD	1.12	2.90
*Rifampin 600 mg QD, 5 days (dose staggered)[6]	40 mg SD	0.20	0.60
*Gemfibrozil 600 mg BID, 7 days	40 mg SD	1.35	1.00
*Fenofibrate 160 mg QD, 7 days	40 mg SD	1.03	1.02
Boceprevir 800 mg TID, 7 days	40 mg SD	2.32	2.66

† Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

* See Sections 5.1 and 7 for clinical significance.

[1] Greater increases in AUC (ratio of AUC up to 2.5) and/or Cmax (ratio of Cmax up to 1.71) have been reported with excessive grapefruit consumption (2 750 mL – 1.2 liters per day).

[2] Ratio based on a single sample taken 8-16 h post dose.

[3] Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

[4] The dose of simultaneously consumed juice in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be much higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

Effects of Colestipol on Other Drugs
Amilodipine

Amlodipine is a weak inhibitor of CYP3A and may increase exposure to CYP3A substrates.

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of atorvastatin, warfarin, and other coumarins.

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethinyl and the warfarin prothrombin response time.

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average 47 -60% increase in trough cyclosporine levels when concomitantly treated with amlodipine *[see Drug Interactions (7.2)]*.

Tacrolimus: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5- to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in increase in dose of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs *[see Drug Interactions (7.2)]*.

Atorvastatin

Table 5 shows the effects of atorvastatin on the pharmacokinetics of other drugs.

Table 5. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen	
	Drug/Dose (mg)	**Ratio of AUC**	**Ratio of Cmax**
80 mg QD for 15 days	Antipyrine, 600 mg SD	1.03	0.89
80 mg QD for 15 days	* Digoxin 0.25 mg QD, 20 days	1.15	1.20
40 mg QD for 22 days	Oral contraceptive QD, 2 months		
	– norethindrone 1 mg	1.28	1.23
	– ethinyl estradiol 35 µg	1.19	1.30
10 mg, SD	†Ipratropium 21 mg INhalaltorvator 200 mg BID, 7 days	1.08	0.96
10 mg QD for 4 days	†Fosamprenavir 1400 mg BID, 14 days	0.73	0.82
10 mg QD for 4 days	†Darunavir/r 700 mg BID/ †ritonavir 100 mg BID, 14 days	0.99	0.94

* See Section 7 for clinical significance.

† See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m² basis, similar to the MRHD of 10 mg amlodipine/day.[1] For the rat, the highest dose level was, on a mg/m² basis, about twice the MRHD.[1]

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the MRHD[1] of 10 mg/day on a mg/m² basis).

[1] Based on patient weight of 50 kg.

Atorvastatin

A 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females; in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, or 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose male and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the CHO mammalian cell assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo micronucleus test.

In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects on fertility. Studies in male rats performed with up to 175 mg/kg (10 times the human exposure) produced no changes in fertility. There was no apiasia and aspermia or teratogenicity in rats given atorvastatin at doses up to approximately a dose equivalent to 100 mg atorvastatin/kg/day for 9 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weights were lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given a dose of atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for two years.

14 CLINICAL STUDIES

14.1 Amlodipine for Hypertension

Adult Patients

The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressure at 24 hours post-dosing, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with baseline pressures of approximately 179/110 mmHg. Diastolic effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 2 parallel, fixed-dose, dose-response studies showed that the reduction in supine and standing blood pressures was dose related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Pediatric Patients

Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 2.5 mg or 5 mg at the end of 8 weeks had significantly lower systolic blood pressure than those secondarily randomized to placebo, averaging about 6 mmHg and 8 mmHg, respectively, for patients weighing less than 50 mmHg systolic and the 5 mg dose and 3.3 mmHg systolic on the 2.5 mg dose. Adverse events were similar to those seen in adults.

14.2 Angina Pectoris Due to CAD

The effectiveness of 5-10 mg amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies, significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine 10 mg, and averaged 7.9% (38 sec) for amlodipine 5 mg. Amlodipine 10 mg also increased time to 1 mm ST segment depression at peak exercise and decreased angina attack rate. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina, there were no clinically significant reductions in blood pressures (-61 mmHg) or changes in heart rate (+0.3 bpm).

14.3 Amlodipine for Vasospastic Angina

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, amlodipine therapy decreased attacks by approximately 4 attacks per week versus 1 attack per week for placebo (p=0.01). Two of 23 amlodipine and 7 of 27 placebo patients discontinued from the study for lack of clinical improvement.

14.4 Amlodipine for Coronary Atherosclerosis

In PREVENT, 825 patients with angiographically documented CAD were randomized to amlodipine 5-10 mg once daily or placebo and followed for 3 years. Although the study did not show significance on the primary objective of change in coronary diameter as assessed by quantitative coronary angiography, the data suggested a favorable outcome with respect to fewer hospitalizations for angina and revascularization procedures in patients with CAD.

CAMELOT enrolled 1318 patients with CAD recently documented by angiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 88% Caucasian, 93% white, all U.S. sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either amlodipine (5-10 mg once daily) or placebo in addition to usual care and were followed for a median of 2.0 years. Most patients (74%), nitroglycerin (50%), antihypertensives (40%), and diuretics (32%), but excluded other calcium channel blockers. The mean duration of follow-up was 14 months. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, myocardial infarction, cardiac arrest, resuscitated cardiac arrest, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease. A total of 110 (16.6%) and 151 (23.1%) first events occurred in the amlodipine and placebo groups, respectively, for a hazard ratio of 0.691 (95% CI: 0.540–0.884, p = 0.003). The primary endpoint is summarized in Figure 1 below. The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularizations (see Table 6). Effects in various subgroups are shown in Figure 2.

In an angiographic substudy (n=274) enrolled at centers PRELIST, there was no significant difference between amlodipine and placebo on the change of atheroma volume in the coronary artery as assessed by intravascular ultrasonic

Figure 1. Kaplan-Meier Analysis of Composite Clinical Outcomes for Amlodipine versus Placebo

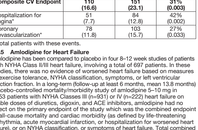


Figure 2. Effects on Primary Endpoint of Amlodipine versus Placebo across Sub Groups

Table 6 below summarizes the significant composite endpoint and clinical outcomes for major subgroups of the primary endpoint. The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, myocardial infarction, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease did not demonstrate a significant difference between amlodipine and placebo.

Table 6. Incidence of Significant Clinical Outcomes for CAMELOT

Clinical Outcomes N (%)	Amlodipine (N=663)	Placebo (N=655)	Risk Reduction (p-value)
Composite CV Endpoint	**110 (16.6)**	**151 (23.1)**	**31% (0.003)**
Hospitalization for Angina*	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization*	78 (11.8)	103 (15.7)	27% (0.033)

* Total patients with these events

14.5 Amlodipine for Heart Failure

Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA Class III-IV heart failure, receiving a total of 697 patients in these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled morbidity/mortality study of amlodipine (5-10 mg in 1153 patients with NYHA Classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, amlodipine had no effect on the primary endpoint of the study which was the combined product of all-cause mortality and morbidity (cardiac arrest, hospitalization for arrhythmia, acute myocardial infarction, hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac mortality were 222/571 (39%) for patients on amlodipine and 246/583 (42%) for patients on placebo; the cardiac mortal events were consistent and about 25% of the morbidity.

Another study (PRAISE-2) randomized patients with NYHA Class III (80%) or IV (20%) heart failure, without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitors (99%), digitalis (99%), and diuretics (99%), to placebo (n=827) or amlodipine (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between amlodipine and placebo in the primary endpoint of all-cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine). With amlodipine, there were more reports of pulmonary edema.

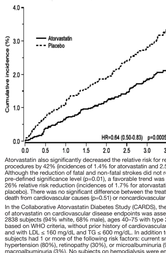
14.6 Amlodipine for Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with total-C levels ≤ 251 mg/dL. All patients had at least three other risk factors at the time of enrollment: male gender (81%), male age ≥ 55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL ≥ 6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP < 140/90 mmHg for non-diabetic patients, < 130/80 mmHg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method that takes into account the distribution of nine baseline characteristics of patients already allocated and minimizes the imbalance of these characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin group)], a relative risk reduction of 36% [Based on incidences of 1.9% for atorvastatin vs. 3.0% for placebo], p=0.0005 (see Figure 3). The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin was seen regardless of baseline LDL levels. Because of the small number of events, results for women were inconclusive.

Figure 3. Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin also significantly reduced the risk for revascularization procedures by 42% (incidences of 1.4% for atorvastatin and 2.5% for placebo). Although the reduction of total mortality (reduction of 23%) did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction in cardiac mortality (0.5% for atorvastatin vs. 0.7% for placebo). There was no significant difference between the treatment groups for death from cardiovascular causes (0.4% for atorvastatin vs. 0.5% for placebo).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on cardiovascular disease was assessed in a population of 2838 subjects (84% white, 68% male), ages 40–75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease, and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (2%). The study compared atorvastatin 10 mg/day versus placebo. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin 10 mg daily (1,429) or placebo (1,411) in a "as soon as possible" approach for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years; mean HbA1c 7.7%; mean LDL-C 120 mg/dL; median total C 207 mg/dL; median TG 101 mg/dL; median HDL-C 52 mg/dL.

The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR (0.63, 95% CI (0.48, 0.83) p=0.001) (see Figure 4). An effect of atorvastatin was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin significantly reduced the risk of stroke by 48% (21 events in the atorvastatin group vs. 38 events in the placebo group), HR (0.52, 95% CI (0.31, 0.88)) p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin group vs. 64 events in the placebo group), HR (0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin group vs. 82 deaths in the placebo group (HR=0.73, p=0.059).

Figure 4. Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Events (Myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 10 mg/day on major cardiovascular events was assessed in 10,001 patients (9,656 (96.5%) male, 38% ≥ 65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level < 130 mg/dL after completing the 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin and followed for a median duration of 4.9 years. The primary endpoint was the time to first occurrence of any of the following major cardiovascular events (MCVE): death from CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL-C levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin.

Treatment with atorvastatin 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p=0.0002 (see Figure 5). The effect of atorvastatin 80 mg/day was consistent regardless of age (< 65, ≥ 65) or gender.

Figure 5. Effect of Atorvastatin 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

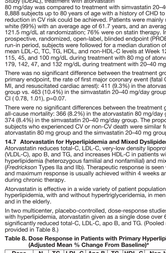


Table 7. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=8232) n (%)	Atorvastatin 80 mg (N=8249) n (%)	HR[a] (95% CI)
PRIMARY ENDPOINT			
First major cardiovascular endpoint	548 (10.9)	434 (8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint			
CHD death	127 (2.5)	101 (2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308 (6.2)	243 (4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	101 (2.0)	117 (2.2)	0.75 (0.58, 0.96)
SECONDARY ENDPOINTS[b]			
First CHF with hospitalization	164 (3.3)	122 (2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282 (5.6)	275 (5.5)	0.97 (0.83, 1.13)
First CABG or other coronary revascularization procedure[c]	921 (18.1)	667 (13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[c]	615 (12.3)	545 (10.8)	0.88 (0.79, 0.98)
All-cause mortality	282 (5.6)	284 (5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality			
Cardiovascular death	155 (3.1)	126 (2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127 (2.5)	158 (3.2)	1.25 (0.99, 1.57)
Cancer death	75 (1.5)	85 (1.7)	1.13 (0.83, 1.53)
Other non-CV death	52 (1.0)	58 (1.2)	1.35 (0.91, 2.03)
Suicide, homicide, and other traumatic non-CV death	9 (0.2)	15 (0.3)	1.67 (0.73, 3.82)

a Atorvastatin 80 mg: atorvastatin 10 mg

b Component of other secondary endpoints

c Secondary endpoints not included in primary endpoint

HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons.

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 80 mg/day reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 7). For the prespecified secondary endpoints, treatment with atorvastatin 80 mg/day significantly reduced the rate of coronary revascularization, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 7). The proportion of patients who underwent a cardiovascular death, including the components of CHD death and fatal stroke, was numerically lower in patients treated with 80 mg of atorvastatin vs. atorvastatin 10 mg treatment groups. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin 80 mg and 10 mg treatment groups, with 80 mg being the largest.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 80 mg/day was compared to treatment with simvastatin 20-40 mg/day in 8888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 67 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL-C levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of atorvastatin and 100, 179, 142, 47, and 132 mg/dL during treatment with 20-40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin 80 mg/day group versus 463 (10.4%) in the simvastatin 20-40 mg/day group, HR 0.88, 95% CI (0.78, 1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 308 (6.9%) in the 80 mg/day group vs. 298 (6.7%) in the 20-40 mg/day group.

There were no significant differences between the treatment groups for all-cause mortality: 308 (6.9%) in the 80 mg/day group vs. 298 (6.7%) in the 20-40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin 80 mg group and the simvastatin 20-40 mg group.

14.7 Atorvastatin for Hypercholesterolemia and Dyslipidemia

Atorvastatin reduces total-C, LDL-C, very low density lipoprotein cholesterol (VLDL-C), apo B, and TG, and in the atherogenic TG-rich lipoproteins in hypertriglyceridemia (hypertriglyceridemia and hyperlipidemia) and mixed dyslipidemia (Fredrickson Types IIa and IIb). Atorvastatin is expected to seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin is effective in a wide variety of patient populations with hyperlipidemia, with and without hypertension, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, atorvastatin given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 8.)

Table 8. Dose Response in Patients with Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)

Dose	N	TC	LDL-C	Apo B	HDL-C	Non-HDL-C/HDL-C
Placebo	21	4	4	3	10	0
10	22	-29	-35	-26	5	-34
20	20	-33	-43	-30	-29	-41
40	21	-37	-50	-42	-29	-45
80	23	-45	-60	-51	-26	-55

* Results are pooled from 2 dose-response studies.

In patients with *Fredrickson Type IIa* primary hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in LDL-C were -41% (-51%, -29%) at 10, 20, 40, and 80 mg were 6.4 (-1.4, 14.8) 7.6 (0, 17), 7.8 (0, 18), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hyperlipidemia, atorvastatin was compared to other statins. After randomization, patients were treated for 16 weeks with atorvastatin 10 mg per day or a fixed dose of the comparative agent (Table 9).

Table 9. Mean Percentage Change from Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7[a]	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff[b]		-9.2, -10.7	-10.0, -12.5	-10.0, -12.5	-15.2, -19.1	-1.7, 0.4	-11.1, -7.1
Diff[b]		-6.5	-8.3	-7.3	-17.1	-0.7	-9.1
Study 2							
Atorvastatin 10 mg	222	-29[a]	-35[a]	-27[a]	-17[a]	+6	-36[a]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[b]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Diff[b]		-8.7	-11.4	-10.4	-7.4	-1.7	-7.8
Study 3							
Atorvastatin 10 mg	132	-29[a]	-37[a]	-34[a]	-23[a]	+7	-39[a]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[b]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9
Diff[b]		-5.7	-6.4	-4.6	-7.9	-0.2	-5.8

[a] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all parameters, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.

[b] Significantly different from lovastatin, ANOVA, p ≤ 0.05

[c] Significantly different from pravastatin, ANOVA, p ≤ 0.05

[d] Significantly different from simvastatin, ANOVA, p ≤ 0.05

The impact on clinical outcomes of the differences in lipid-altering effects between treatments is unknown. Table 9 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

14.8 Atorvastatin for Homozygous Familial Hypercholesterolemia

The response to atorvastatin in 64 patients with isolated hyperlipidemia (Fredrickson Type IV) treated in 5 clinical trials, including 2 controlled trials, is shown in the table below (Table 10). For the atorvastatin-treated patients, median (min, max) baseline TG were 565 (267–1922).

Table 10. Combined Patients with Isolated Elevated TG: Median (min, max) Percentage Change from Baseline

	Placebo (n=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 40 mg (N=14)
TG	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-51.0 (-82.7, 29.5)	-57.5 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-29.0 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-28.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	13.8 (-18.6, 13.4)	-7.2 (-9.7, 61.5)	-8.8 (-3.2, 25.2)	-7.2 (-10.8, 57.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-54.5 (-62.2, -10.8)	-57.5 (-88.2, 67.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-38.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

14.10 Atorvastatin for Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 years and older with HoFH received atorvastatin titrated up to 80 mg daily. The mean TC in the population of this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 1% to 53%; median